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14. ABSTRACT
The **purpose** of this project is to identify predictive markers of heterotopic ossification in an established animal model that would forecast development of HO in humans soon after injury. Since relocation to MUSC, the PI has been fully engaged in securing suitable facilities and related institutional and state regulatory approvals to implement the animal blast model at MUSC. This was accomplished in July 2014, nearly 15 months after the PI's arrival on 1 April, 2013. Blast procedures have been completed on all 30 animals in the year 1 SOW; they are now nearly 3 months post-blast and are being survived and followed according to protocol with scheduled biopsies and routine radiographs to monitor progression of HO. Specimen samples have been obtained and are under analysis for identification of protein biomarkers. Year 2 SOW animal procedures will begin on schedule in the fifth quarter of the award.

15. SUBJECT TERMS
Heterotopic ossification, blast injury, amputation, bone formation, animal model, rat model, gene expression, protein expression, biomarkers

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Introduction:

Heterotopic ossification (HO), characterized by the pathologic formation of mature bone in the soft tissues, is a frequent complication following high energy orthopaedic trauma. HO is prevalent in patients with severe extremity war-time wounds; specifically, its incidence is reported as high as 57% in patients that sustain a poly-trauma blast injury [1]. Complications related to HO in residual limbs following blast amputation include pain, overlying skin and muscle breakdown, poor fitting and functioning of prosthetic limbs, reoperation for amputation revision, and impaired limb function that delays or limits rehabilitation [2-6]. Current treatments to prevent HO are limited to mitigation rather than prevention. Furthermore, removal of heterotopic bone after it has formed can be difficult; this frequently requires resection of substantial amounts of soft tissue and risks injury to adjacent neurovascular structures that are often intimately associated with the ectopic bone. It is preferable to address the issue of HO before it begins. Prevention of HO in residual limbs is needed to offer amputation survivors the best possible quality of life and return to function. We have developed a blast amputation animal model and validated that it replicates the human condition with respect to formation of HO. The current studies are directed at identifying early-appearing biomarkers in the animal model that predict the occurrence of HO in the animal model and may well similarly predict the development of HO in the human condition. Patients exhibiting biomarkers predictive of exuberant HO formation can then be identified before the disease process begins and treated prophylactically.

Keywords:
Heterotopic ossification, blast injury, amputation, bone formation, animal model, rat model, gene expression, protein expression, biomarkers

Overall Project Summary:

Current objectives: We have completed all thirty hind-limb blast amputation procedures indicated for Task 1 of Specific Aim 1. These animals are now being survived out 24 weeks and followed with serial x-rays. Fifteen of the animals underwent bilateral muscle biopsy procedure at two weeks and fifteen underwent biopsy procedure at four weeks, as per protocol. The biopsy specimens are currently being analyzed for both gene- and protein-level biomarkers and will be compared to gene expression signatures in existing human tissue samples known to be characteristic for the formation of heterotopic ossification.

Results: Biomarker analysis, from two- and four-week biopsy specimens to identify molecular predictors of HO, is currently underway on the first group of sixty biopsy specimens. There are no results available at this time.

Progress and Accomplishments: Facilities have been established for conduct of the blast model at MUSC and all necessary institutional and state regulatory approvals have been obtained. We have completed all hind-limb blast amputation procedures

on 30 animals, with 100% animal survival, as well as related scheduled biopsies included in Task 1 of Specific Aim 1. The project is currently on schedule and Task 2 work will occur in the 5th quarter as planned. We do not anticipate any delays affecting the study in the near future.

Key Research Accomplishments: Nothing to report.

Conclusion: Research work now on schedule as proposed and planned.

Publications, Abstracts, and Presentations: Nothing to report.

Inventions, Patents and Licenses: Nothing to report.

Reportable Outcomes: Nothing to report.

Other Achievements: A pre-application has been submitted (10.8.2014) in response to the "Expansion Award" opportunity and solicitation related to this work. The experience and training provided by this award during the prior year directly contributed to the successful hiring of the past research resident to a position in the Orthopaedic residency at the Medical University of South Carolina.

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Appendices: None